

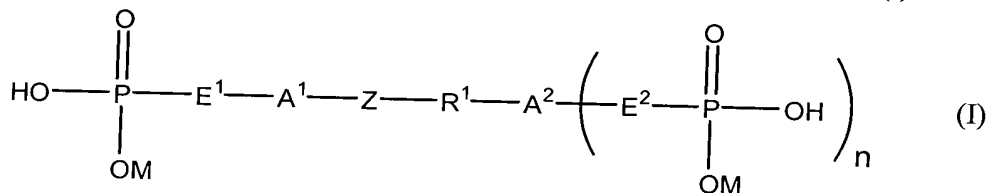
is attached hereto in an addendum entitled "ADDENDUM TO PRELIMINARY AMENDMENT DATED APRIL 8, 2002". In this addendum, changes are indicated by underlining added text and by striking out deleted text.

In the Claims:

Cancel claims 1-20.

Add new claims 21-77, as follows:

(21) A method for inhibiting activity of an alkaline phosphatase, said method comprising contacting the alkaline phosphatase with a compound of formula (I):



where:

$\text{A}^1$  and  $\text{A}^2$  are the same or different aryl groups collectively bearing at least one hydrophilic substituent;

$\text{E}^1$  and  $\text{E}^2$  are the same or different and are O, S, or  $\text{NR}^2$  (where  $\text{R}^2$  is H or a linear or branched  $\text{C}_1\text{-C}_{20}$  carbon containing group);

M is H or a pharmaceutically acceptable monovalent cation;

$\text{R}^1$  is a linear or branched, saturated or unsaturated,  $\text{C}_1\text{-C}_{20}$  carbon containing group;

Z is a single bond, a carbonyl,  $\text{CE}^3\text{E}^4$ , or  $\text{CR}^3\text{E}^4$ , where

$\text{E}^3$  and  $\text{E}^4$  are the same or different and are  $\text{OR}^4$ ,  $\text{SR}^4$ , and  $\text{NR}^4_2$ , where

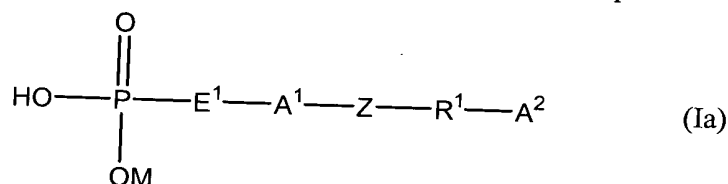
$\text{R}^3$  is a linear or branched  $\text{C}_1\text{-C}_{20}$  carbon containing group, and

$\text{R}^4$  is H or a linear or branched  $\text{C}_1\text{-C}_{20}$  carbon containing group; and

n is 0 or 1,

or a pharmaceutically acceptable salt thereof under conditions effective to inhibit the alkaline phosphatase's activity.

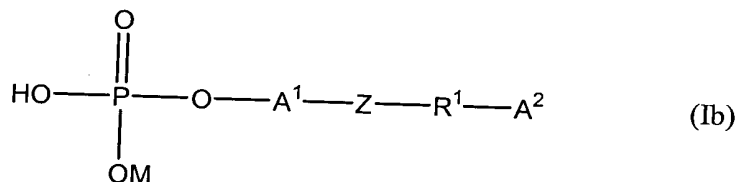
22. The method of claim 21 where the compound is a compound of formula (Ia):



where:

A<sup>1</sup>, A<sup>2</sup>, E<sup>1</sup>, M, R<sup>1</sup> and Z are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

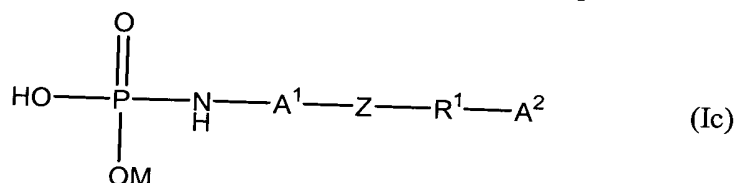
23. The method of claim 21 where the compound is a compound of formula (Ib):



where:

A<sup>1</sup>, A<sup>2</sup>, E<sup>1</sup>, M, R<sup>1</sup> and Z are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

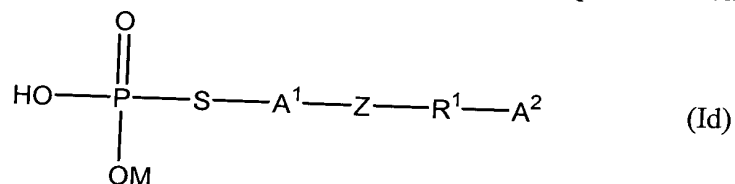
24. The method of claim 21 where the compound is a compound of formula (Ic):



where:

A<sup>1</sup>, A<sup>2</sup>, M, R<sup>1</sup> and Z are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

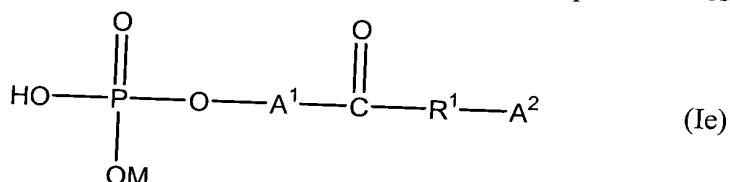
25. The method of claim 21 where the compound is a compound of formula (Id):



where:

A<sup>1</sup>, A<sup>2</sup>, M, R<sup>1</sup> and Z are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

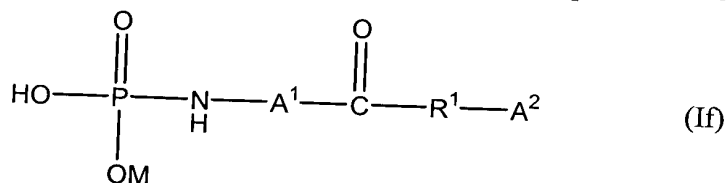
26. The method of claim 21 where the compound is a compound of formula (Ie):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

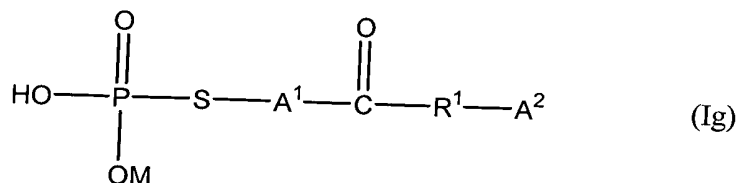
27. The method of claim 21 where the compound is a compound of formula (If):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

28. The method of claim 21 where the compound is a compound of formula (Ig):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

29. The method of claim 21 where the compound is a compound is 2'-phosphophloretin, 2'-thiophosphophloretin, 2'-aminophosphophloretin, 3-azido-2'-phosphophloretin, or 4-azido-2'-phosphophloretin or a pharmaceutically acceptable salt thereof.

30. The method of claim 21, wherein the compound is not 4'-phosphophloretin or a pharmaceutically acceptable salt thereof.

31. The method of claim 21, wherein, when E<sup>1</sup> is O and when Z is a carbonyl and when A<sup>1</sup> is a phenyl ring and when E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup> and when the phenyl ring A<sup>1</sup> is further substituted in the 4- and 6- positions thereof with OR<sup>5</sup> groups (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms), A<sup>2</sup> is not a phenyl ring substituted in the 4-position thereof with an OR<sup>5</sup> group (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms).

32. The method of claim 31, wherein, when E<sup>1</sup> is O and when Z is a carbonyl and when A<sup>1</sup> is a phenyl ring and when E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>, A<sup>1</sup> is not further substituted in the 4- and 6-positions of the phenyl ring A<sup>1</sup> with OR<sup>5</sup> groups (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms).

33. The method of claim 21, wherein E<sup>1</sup> is O and wherein A<sup>2</sup> is a phenyl ring bearing an OH group in the 4-position thereof.

34. The method of claim 21, wherein E<sup>1</sup> is O; wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with an OH group in the 4-position thereof.

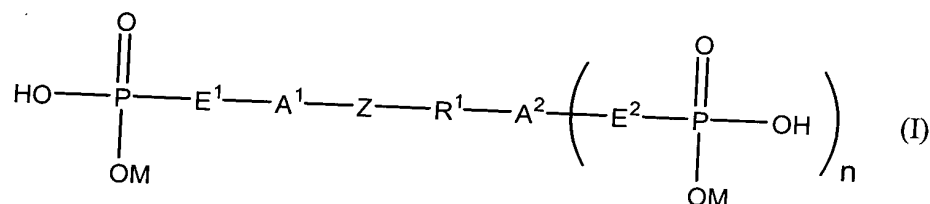
35. The method of claim 21, wherein E<sup>1</sup> is O and wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with an OH group in the 6-position thereof.

Alc 36. The method of claim 21, wherein E<sup>1</sup> is O and wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with OH groups in the 4- and 6-positions thereof.

37. The method of claim 21, wherein E<sup>1</sup> is O; wherein A<sup>2</sup> is a phenyl ring bearing an OH group in the 4-position thereof; wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with OH groups in the 4- and 6-positions thereof.

38. The method of claim 21, wherein A<sup>1</sup> is a phenyl ring and E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>.

39. A method for inhibiting activity of an alkaline phosphatase in a subject, said method comprising administering to the subject a compound of formula (I):



where:

$\text{A}^1$  and  $\text{A}^2$  are the same or different aryl groups collectively bearing at least one hydrophilic substituent;

$\text{E}^1$  and  $\text{E}^2$  are the same or different and are O, S, or  $\text{NR}^2$  (where  $\text{R}^2$  is H or a linear or branched  $\text{C}_1$ - $\text{C}_{20}$  carbon containing group);

M is H or a pharmaceutically acceptable monovalent cation;

$\text{R}^1$  is a linear or branched, saturated or unsaturated,  $\text{C}_1$ - $\text{C}_{20}$  carbon containing group;

Z is a single bond, a carbonyl,  $\text{CE}^3\text{E}^4$ , or  $\text{CR}^3\text{E}^4$ , where

$\text{E}^3$  and  $\text{E}^4$  are the same or different and are  $\text{OR}^4$ ,  $\text{SR}^4$ , and  $\text{NR}^4_2$ , where

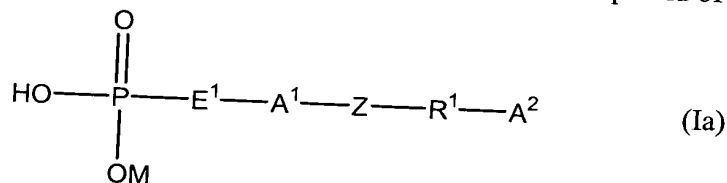
$\text{R}^3$  is a linear or branched  $\text{C}_1$ - $\text{C}_{20}$  carbon containing group, and

$\text{R}^4$  is H or a linear or branched  $\text{C}_1$ - $\text{C}_{20}$  carbon containing group; and

n is 0 or 1,

or a pharmaceutically acceptable salt thereof.

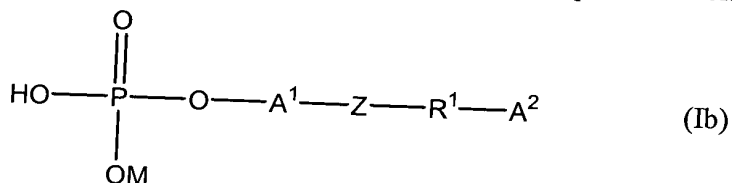
40. The method of claim 39 where the compound is a compound of formula (Ia):



where:

$\text{A}^1$ ,  $\text{A}^2$ ,  $\text{E}^1$ , M,  $\text{R}^1$  and Z are as defined in claim 21, or a pharmaceutically acceptable salt thereof.

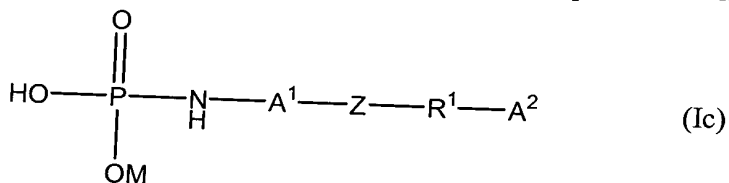
41. The method of claim 39 where the compound is a compound of formula (Ib):



where:

A<sup>1</sup>, A<sup>2</sup>, E<sup>1</sup>, M, R<sup>1</sup> and Z are as defined in claim 39, or a pharmaceutically acceptable salt thereof.

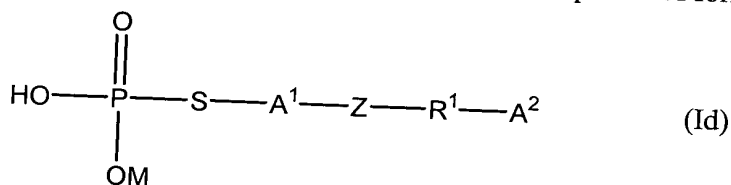
42. The method of claim 39 where the compound is a compound of formula (Ic):



where:

A<sup>1</sup>, A<sup>2</sup>, M, R<sup>1</sup> and Z are as defined in claim 39, or a pharmaceutically acceptable salt thereof.

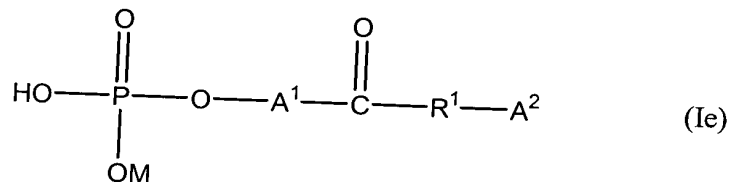
43. The method of claim 39 where the compound is a compound of formula (Id):



where:

A<sup>1</sup>, A<sup>2</sup>, M, R<sup>1</sup> and Z are as defined in claim 39, or a pharmaceutically acceptable salt thereof.

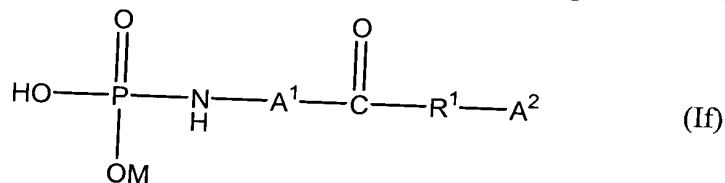
44. The method of claim 39 where the compound is a compound of formula (Ie):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 39, or a pharmaceutically acceptable salt thereof.

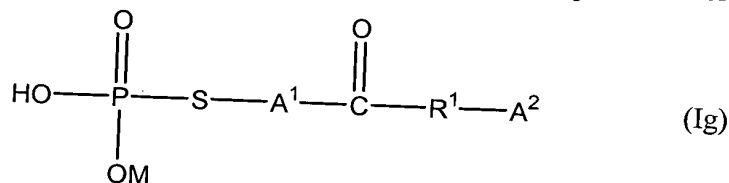
45. The method of claim 39 where the compound is a compound of formula (If):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 39, or a pharmaceutically acceptable salt thereof.

46. The method of claim 39 where the compound is a compound of formula (Ig):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 39, or a pharmaceutically acceptable salt thereof.

47. The method of claim 39 where the compound is a compound is 2'-phosphophloretin, 2'-thiophosphophloretin, 2'-aminophosphophloretin, 3-azido-2'-



phosphophloretin, or 4-azido-2'-phosphophloretin or a pharmaceutically acceptable salt thereof.

48. The method of claim 39, wherein the compound is not 4'-phosphophloretin or a pharmaceutically acceptable salt thereof.

49. The method of claim 39, wherein, when E<sup>1</sup> is O and when Z is a carbonyl and when A<sup>1</sup> is a phenyl ring and when E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup> and when the phenyl ring A<sup>1</sup> is further substituted in the 4- and 6- positions thereof with OR<sup>5</sup> groups (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms), A<sup>2</sup> is not a phenyl ring substituted in the 4-position thereof with an OR<sup>5</sup> group (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms).

50. The method of claim 49, wherein, when E<sup>1</sup> is O and when Z is a carbonyl and when A<sup>1</sup> is a phenyl ring and when E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>, A<sup>1</sup> is not further substituted in the 4- and 6-positions of the phenyl ring A<sup>1</sup> with OR<sup>5</sup> groups (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms).

51. The method of claim 39, wherein E<sup>1</sup> is O and wherein A<sup>2</sup> is a phenyl ring bearing an OH group in the 4-position thereof.

52. The method of claim 39, wherein E<sup>1</sup> is O; wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with an OH group in the 4-position thereof.

53. The method of claim 39, wherein E<sup>1</sup> is O and wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with an OH group in the 6-position thereof.

54. The method of claim 39, wherein E<sup>1</sup> is O and wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with OH groups in the 4- and 6-positions thereof.

55. The method of claim 39, wherein E<sup>1</sup> is O; wherein A<sup>2</sup> is a phenyl ring bearing an OH group in the 4-position thereof; wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with OH groups in the 4- and 6-positions thereof.

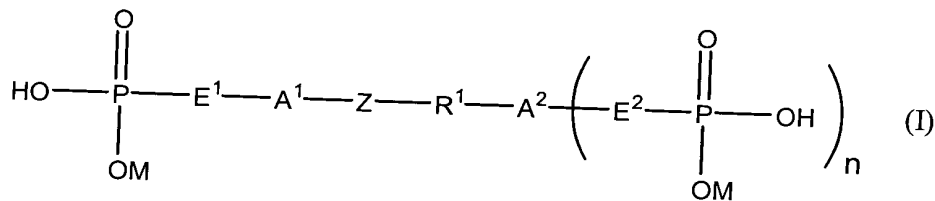
56. The method of claim 39, wherein A<sup>1</sup> is a phenyl ring and E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>.

57. The method of claim 39, where the administration is intermittent.

58. The method of claim 39, where the administration is oral.

59. The method of claim 39, where the administration is parenteral.

60. A method for inhibiting sodium-mediated phosphate uptake, said method comprising contacting a compound of formula (I):



where:

A<sup>1</sup> and A<sup>2</sup> are the same or different aryl groups collectively bearing at least one hydrophilic substituent;

$E^1$  and  $E^2$  are the same or different and are O, S, or  $NR^2$  (where  $R^2$  is H or a linear or branched  $C_1$ - $C_{20}$  carbon containing group);

M is H or a pharmaceutically acceptable monovalent cation;

$R^1$  is a linear or branched, saturated or unsaturated,  $C_1$ - $C_{20}$  carbon containing group;

Z is a single bond, a carbonyl,  $CE^3E^4$ , or  $CR^3E^4$ , where

$E^3$  and  $E^4$  are the same or different and are  $OR^4$ ,  $SR^4$ , and  $NR^4_2$ , where

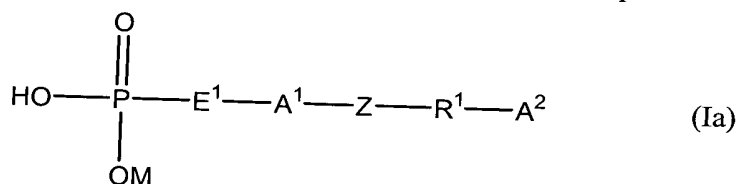
$R^3$  is a linear or branched  $C_1$ - $C_{20}$  carbon containing group, and

$R^4$  is H or a linear or branched  $C_1$ - $C_{20}$  carbon containing group; and

n is 0 or 1,

or a pharmaceutically acceptable salt thereof, with intestinal brush border membrane under conditions effective to inhibit sodium-mediated phosphate uptake.

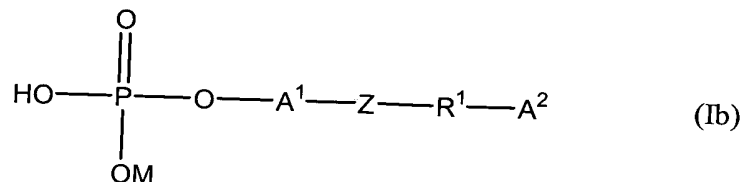
61. The method of claim 60 where the compound is a compound of formula (Ia):



where:

$A^1$ ,  $A^2$ ,  $E^1$ , M,  $R^1$  and Z are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

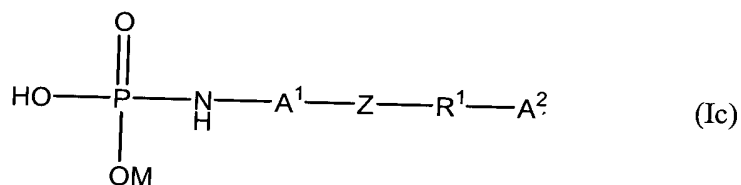
62. The method of claim 60 where the compound is a compound of formula (Ib):



where:

A<sup>1</sup>, A<sup>2</sup>, E<sup>1</sup>, M, R<sup>1</sup> and Z are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

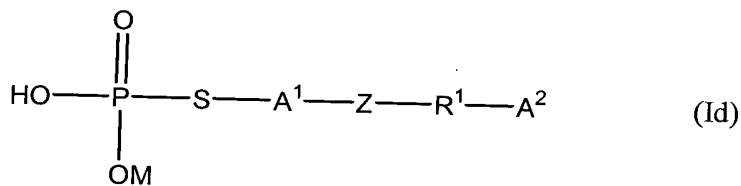
63. The method of claim 60 where the compound is a compound of formula (Ic):



where:

A<sup>1</sup>, A<sup>2</sup>, M, R<sup>1</sup> and Z are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

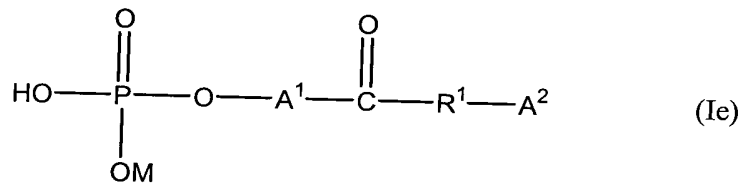
64. The method of claim 60 where the compound is a compound of formula (Id):



where:

A<sup>1</sup>, A<sup>2</sup>, M, R<sup>1</sup> and Z are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

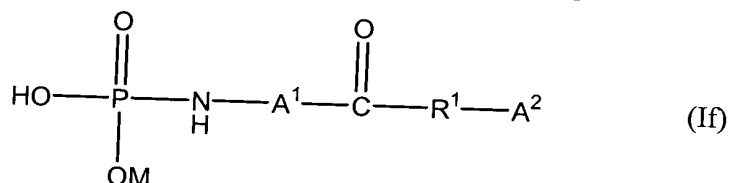
65. The method of claim 60 where the compound is a compound of formula (Ie):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

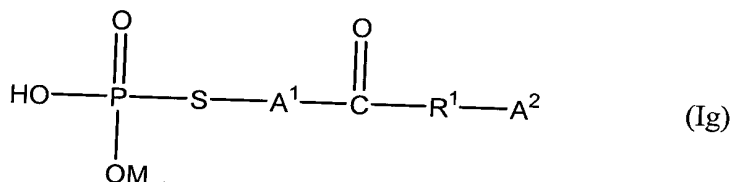
66. The method of claim 60 where the compound is a compound of formula (If):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

67. The method of claim 60 where the compound is a compound of formula (Ig):



where:

A<sup>1</sup>, A<sup>2</sup>, M, and R<sup>1</sup> are as defined in claim 60, or a pharmaceutically acceptable salt thereof.

68. The method of claim 60 where the compound is a compound is 2'-phosphophloretin, 2'-thiophosphophloretin, 2'-aminophosphophloretin, 3-azido-2'-phosphophloretin, or 4-azido-2'-phosphophloretin or a pharmaceutically acceptable salt thereof.

69. The method of claim 60, wherein the compound is not 4'-phosphophloretin or a pharmaceutically acceptable salt thereof.

70. The method of claim 60, wherein, when E<sup>1</sup> is O and when Z is a carbonyl and when A<sup>1</sup> is a phenyl ring and when E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup> and when the phenyl ring A<sup>1</sup> is further substituted in the 4- and 6- positions thereof with OR<sup>5</sup> groups (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms), A<sup>2</sup> is not a phenyl ring substituted in the 4-position thereof with an OR<sup>5'</sup> group (where R<sup>5'</sup> is a carbon containing group having between 1 and 4 carbon atoms).

71. The method of claim 70, wherein, when E<sup>1</sup> is O and when Z is a carbonyl and when A<sup>1</sup> is a phenyl ring and when E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>, A<sup>1</sup> is not further substituted in the 4- and 6-positions of the phenyl ring A<sup>1</sup> with OR<sup>5</sup> groups (where R<sup>5</sup> is a carbon containing group having between 1 and 4 carbon atoms).

72. The method of claim 60, wherein E<sup>1</sup> is O and wherein A<sup>2</sup> is a phenyl ring bearing an OH group in the 4-position thereof.

73. The method of claim 60, wherein E<sup>1</sup> is O; wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with an OH group in the 4-position thereof.

74. The method of claim 60, wherein E<sup>1</sup> is O and wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with an OH group in the 6-position thereof.

75. The method of claim 60, wherein E<sup>1</sup> is O and wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with OH groups in the 4- and 6-positions thereof.

76. The method of claim 60, wherein E<sup>1</sup> is O; wherein A<sup>2</sup> is a phenyl ring bearing an OH group in the 4-position thereof; wherein A<sup>1</sup> is a phenyl ring; wherein E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>; and wherein the phenyl ring A<sup>1</sup> is further substituted with OH groups in the 4- and 6-positions thereof.

77. The method of claim 60, wherein A<sup>1</sup> is a phenyl ring and E<sup>1</sup> is at the 2-position of the phenyl ring A<sup>1</sup>.

Respectfully submitted,

April 8, 2002  
Date

Peter Rogalskyj  
Peter Rogalskyj  
Reg. No. 38,601

Braman & Rogalskyj, LLP  
P.O. Box 352  
Canandaigua, New York 14424-0352  
Tel: 716-393-3004  
Fax: 716-393-3001

